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Synthesis of functionalized β-lactams and pyrrolidine-2, 5-diones through Metal-free sequential Ugi-4CR/ cyclization

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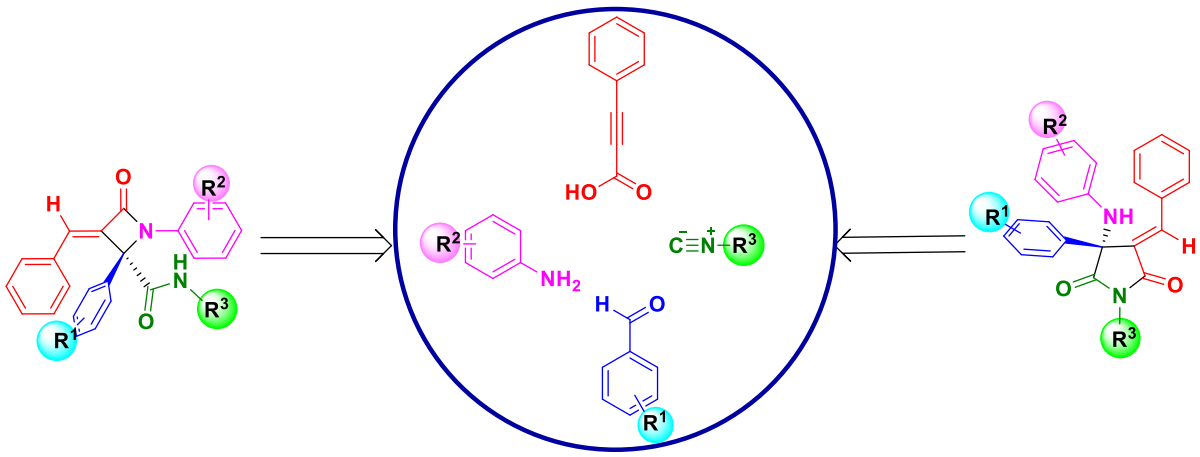


Abstract:

An efficient approach for the synthesis of functionalized *β*-lactams and pyrrolidine-2,5-diones was achieved through sequential Ugi-4CR/cyclization reaction. Diversity-oriented synthesis, good to high yields, easy work-up and short reaction times are advantages of this procedure.

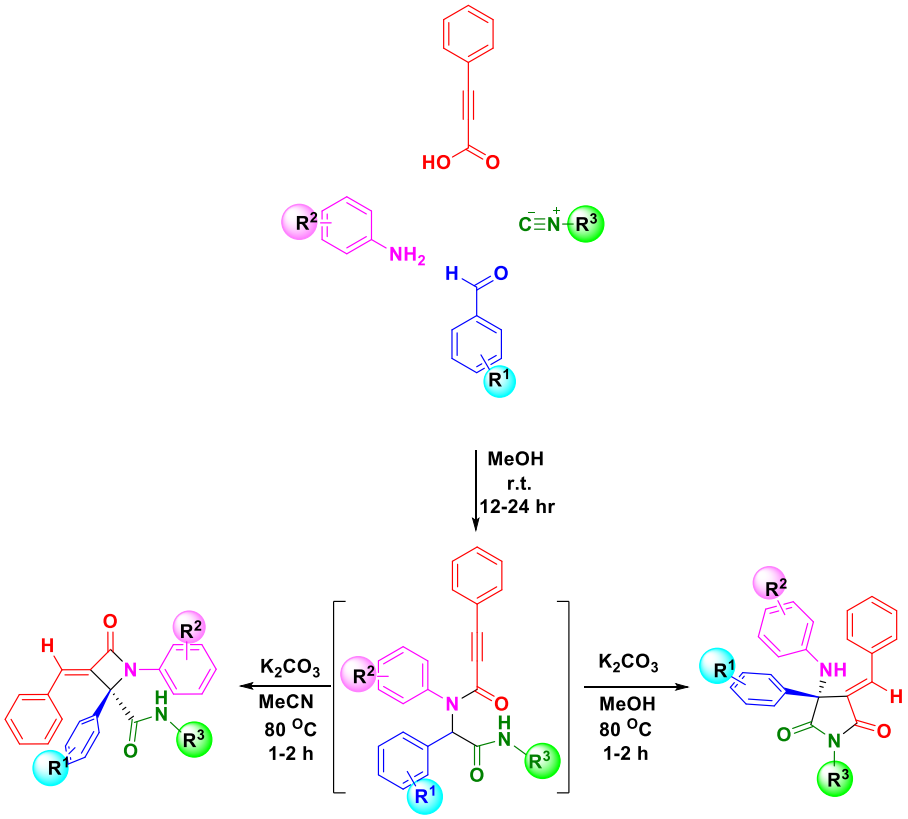
Keywords: Sequential Ugi-4CR/ cyclization, Ugi post-transformation, *β*-lactams, pyrrolidine-2, 5-diones, Metal-free reaction

Introduction

Synthesis of molecules with high diversity and complexity using readily available starting materials is an interesting approach in combinatorial chemistry and drug discovery. In this regard, combining the multicomponent reactions (MCRs) with post MCR transformation has been used as an efficient method for the synthesis of highly functionalized compounds.[1] Among these sequential reactions, Ugi-4CR/post transformation is the most powerful approach for the synthesis of polyfunctional compounds.[2]

N-substituted-2-alkynamides have proved to be valuable building blocks in organic synthesis.[3] In recent years, some functionalized *N*-substituted-2-alkynamides were synthesized through Ugi-4CR in our research group. These compounds were used for further post-transformation reactions such as nucleophilic addition or cyclization using suitable starting materials and palladium catalysts.[4] Recently, Van der Eycken used these starting materials to construct heterocyclic skeletons in the presence of different gold catalysts.[5] Meanwhile , palladium catalyst was used for the transition-metal catalyzed cycloisomerization of alkynyl *N*-acyl enamines to access lactams.[6] Zhang *et al*. reported a highly enantioselective cycloisomerization approach to access functionalized lactams using Rh based catalysts. [7] Due to the biological activities of lactams,[8] finding the new method that allows formation of C-N bond and stereoselective generation of functionalized lactams is an interesting subject in organic synthesis. In all the reported cyclization reactions with these starting materials, use of a metal catalyst is necessary. But, development of metal-free approach is an interesting challenge in organic synthesis.[9] Ugi/post-transformation has been reported for the for the synthesis of *β*-lactams, but the using of functionalized starting materials has an important role in cyclization reaction process.[10]

In continuation of our previous research works based on the cyclization reactions of functionalized *N*-substituted-2-alkynamides,[4] we were encouraged to investigate the cyclization products through these compounds in metal-free reaction conditions. Herein, we report a metal-free cyclization through sequential Ugi-4CR/cyclization reaction for the synthesis of functionalized *β*-lactams and pyrrolidine-2,5-diones.

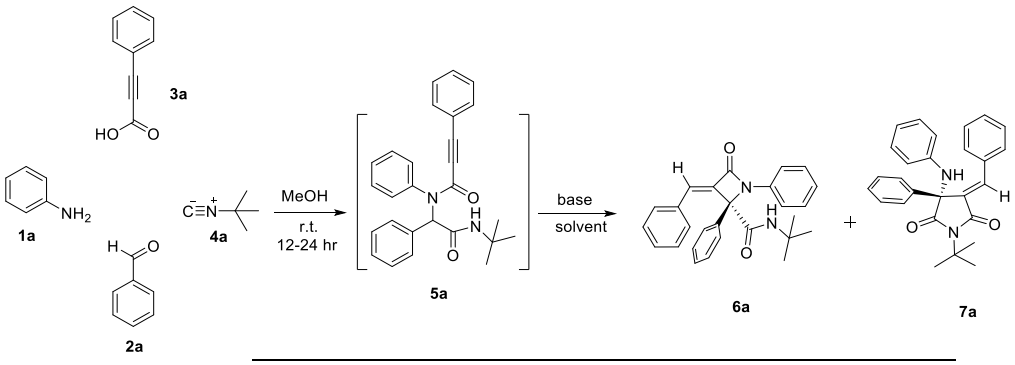


Scheme 1. Synthesis of β-lactams and pyrrolidine-2, 5-diones through metal-free sequential Ugi-4CR/ cyclization

Results and Discussion

In the first step, Ugi-4CR of benzaldehyde, aniline, *tert*-butyl isocyanide and phenyl propiolic acid was chosen as the model reaction. The *N*-substituted 2-alkynamide **5a** was precipitated and separated, followed by the treatment with different bases and solvents. During the optimization of the reaction conditions, it was revealed that potassium carbonate (K_2CO_3) was the most effective base to provide cyclization products compared to other bases. (Table 1, entries 8-11) Carrying out the reaction in acetonitrile led to the synthesis of *β*-lactam **6a** and in methanol the sole product was pyrrolidine-2,5-dione **7a**. (Table 1) With our optimized reaction conditions in hand, carrying out the reaction in DMF led to a mixture of two products **6a** and **7a** (75:25), respectively.

Table 1. Optimization of reaction conditions for the synthesis of *β*-lactam **6a** and pyrrolidine-2,5-dione **7a**.



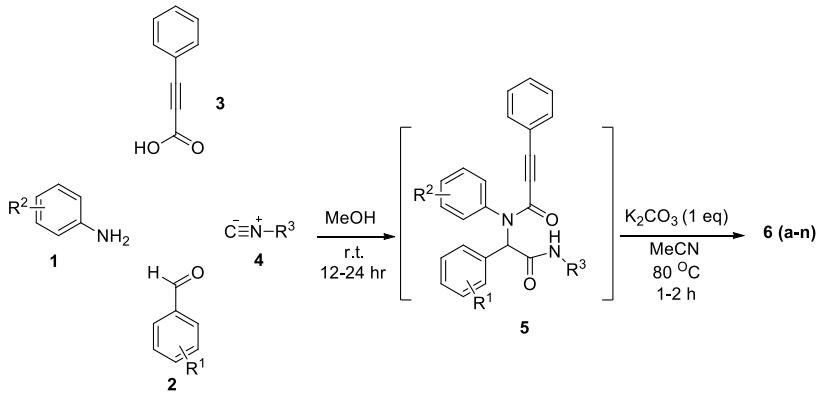
Entry	base	solvent	T (°C)	6a (%)	7a (%)
1	K_2CO_3	CH_2Cl_2	Rt	-	-
2	K_2CO_3	MeCN	80	95	-
3	K_2CO_3	DMF	120	75	25
4	K_2CO_3	THF	Reflux	-	-
5	K_2CO_3	H_2O	Reflux	-	-
6	K_2CO_3	Toluene	Reflux	-	-
7	K_2CO_3	MeOH	Reflux	-	94
8	Cs_2CO_3	MeOH	Reflux	-	54
9	CsOAc	MeOH	Reflux	-	-
10	Et_3N	MeOH	Reflux	trace	-
11	DIEA	MeOH	Reflux	10	-

The reaction was performed using **1a** (1 mmol), **2a** (1 mmol), **3a** (1 mmol), **4a** (1 mmol), the base (1 eq) and 5 ml of solvent.

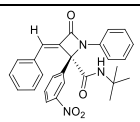
On the basis of this information and in order to explore the above reaction scope, different aldehydes, anilines and isocyanides were used as starting materials. In all cases, the *β*-lactam skeleton with some functional groups was produced in good to high yields. The results are summarized in table 2. The products with *β*-lactam skeleton (**6a-n**) were obtained in 63-95% yields. The lowest yield (63%) was obtained for compound **6g** which trifluoromethyl benzaldehyde was used as aldehyde and cyclohexyl isocyanide as isocyanide. A significant

point in formation of *β*-lactams is the E-geometry for double bond in all cases. It seems that the secondary interaction (π- π stacking) could affect the geometry of formed *β*-lactams.

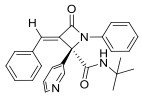
Table 2. Synthesis of functionalized β-lactams 6(a-n) through sequential Ugi 4-CR/cyclization



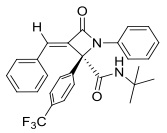
6a (94%)



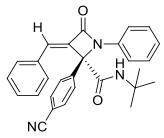
6b (74%)



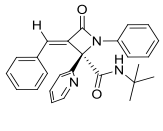
6c (89%)



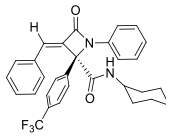
6d (82%)



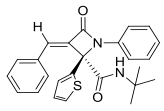
6e (66%)



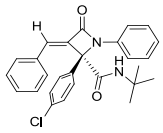
6f (64%)



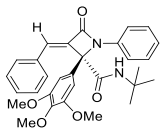
6g (63%)



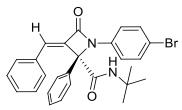
6h (90%)



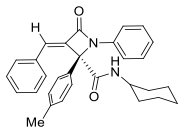
6i (95%)



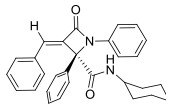
6j(80%)



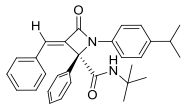
6k (94%)



6l (83%)



6m (89%)



6n (87%)

X-ray crystallographic data could confirm the structure. Double bond has *E* configuration and orientation of two aryl group has a suitable condition for π-π stacking. (Figure 1)

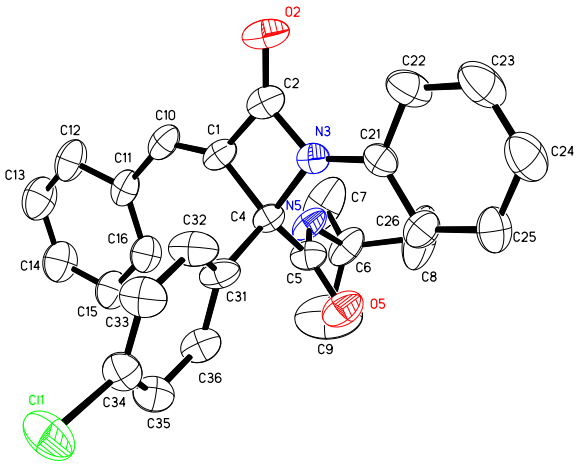
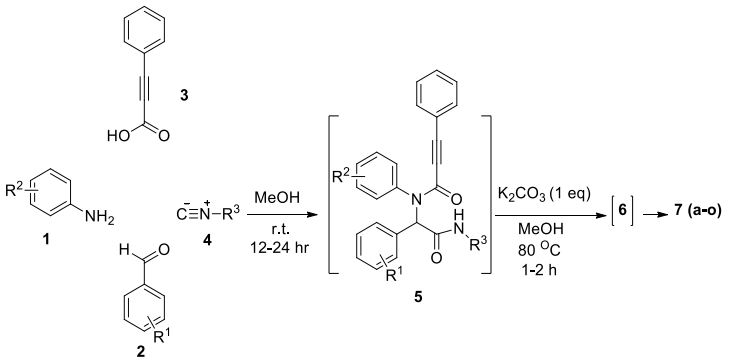
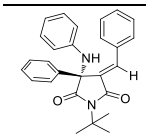


Figure 1. ORTEP structure of compound **6i**

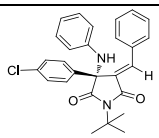
After finding the best reaction condition in hand, we screened a range of *N*-substituted-2-alkynamides in one-pot sequential Ugi-4CR/intramolecular nucleophilic cyclization in methanol. The results are summarized in table 3. The obtained products were pyrrolidine-2,5-diones with regioselectivity **7a-o** and the double bond in the structure of products had *E* configuration. The progress of reactions were monitored by TLC, and comparison of data showed that the pyrrolidine-2,5-dione **7a** was produced through *β*-lactam intermediate in high yield.

Table 3. Synthesis of pyrrolidine-2,5-dione derivatives **7(a-o)** through sequential Ugi 4CR/Cyclization *via* β-lactam **6** intermediate

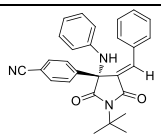




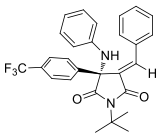
7a (94%)



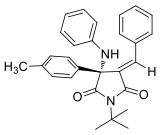
7b (91%)



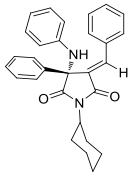
7c (84%)



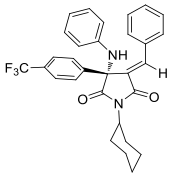
7d (97%)



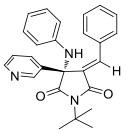
7e (86%)



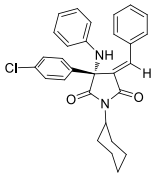
7f (83%)



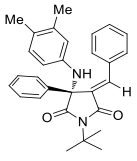
7g (90%)



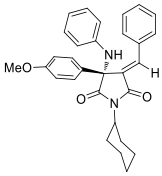
7h (68%)



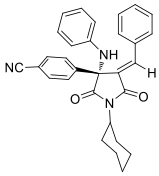
7i (88%)



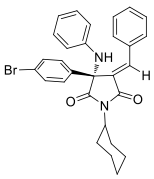
7j (76%)



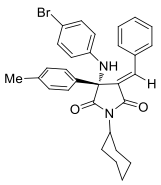
7k (82%)



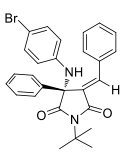
7l (72%)



7m (81%)



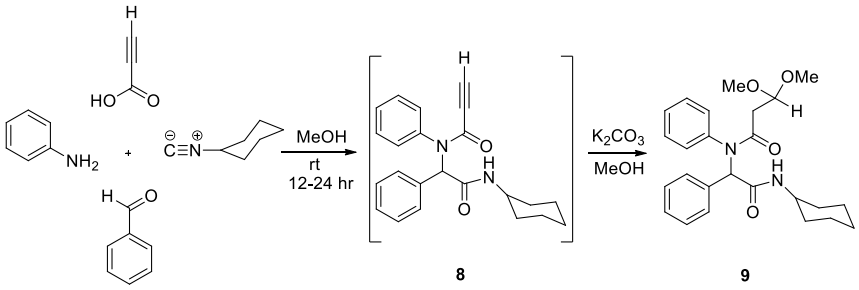
7n (83%)



7o (74%)

The structures of **6(a-n)** and **7(a-o)** were assigned by ^{1}H-NMR and ^{13}C-NMR spectroscopy and also proved by ESI-HRMS. There are two prominent differences in the NMR spectra of these two sets of compounds. The first one is the highly characteristic peak at 4-5 ppm for NH in pyrrolidine-2,5-dione which was not observed in *β*-lactam derivatives. The second one is the difference in the chemical shift of carbonyl amide in *β*-lactam (162-166 ppm) and pyrrolidine-2,5-dione (170-176 ppm). For two compounds **7b** and **7d** the ORTEP structure could confirm the products. (Supporting information) The ^{1}H-^{1}H-COSY 2D NMR was used for determining of the structure of compounds. The 2D ^{1}H NMR of the compounds **6n** and **7m** were provided as attachment in supporting information section.

In another try, the reaction was investigated using propiolic acid instead of phenyl propiolic acid. In this case, the intermediate **8** could not convert to the desired pyrrolidine-2,5-dione and MeOH was added to the triple bond.

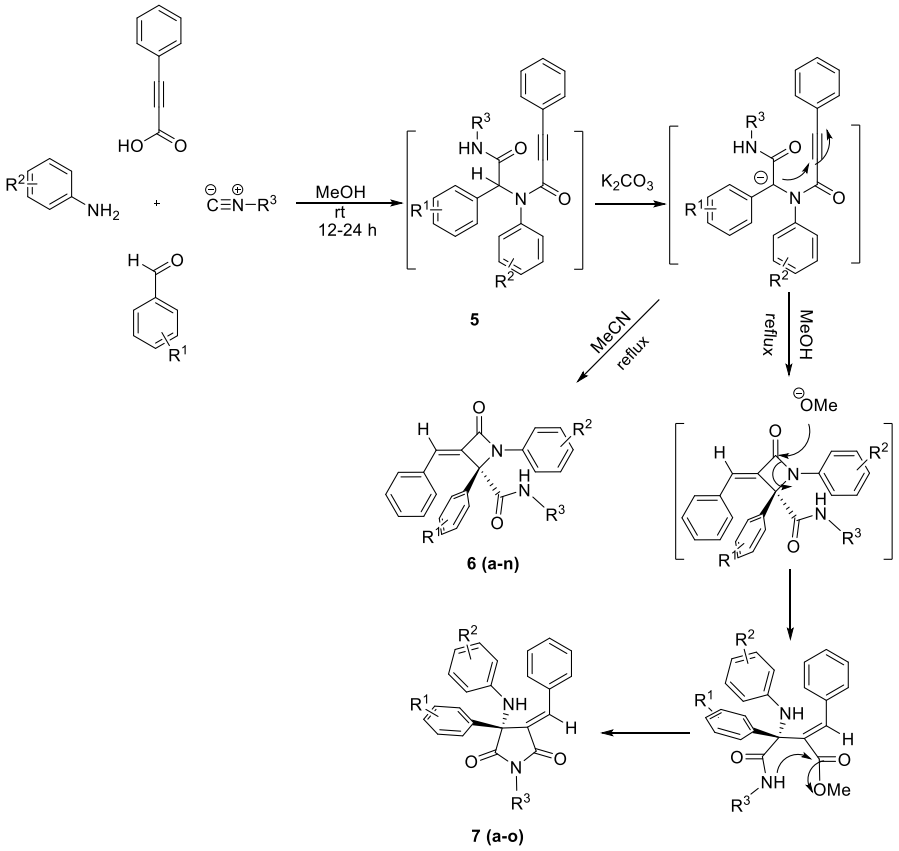


Scheme 2. Nucleophilic addition of methanol to *N*-substituted-2-alkynamide 8 and formation of unexpected product 9

The same reaction was also checked with 2-butyn-oic acid and trimethylsilyl propiolic acid in methanol and the desired products were not formed. The structure of product was confirmed based on the NMR spectra. According to the NMR data, when 2-butyn-oic acid was used the reaction in methanol led to the methyl ether. The Ugi-4CR was carried out using trimethylsily propiolic acid and its reaction was studied in methanol in the presence of potassium carbonate which led to the acetal **9** with the elimination of trimethylsilyl group.

In the structure of functionalized *N*-substituted 2-alkynamides **5**, there are two amide moieties, triple bond and also a C-H bond. The C-H bond has an acidic character which could be deprotonated using a suitable base and form the carbanion which in turn could be added to the triple bond through intramolecular nucleophilic addition. A plausible mechanism for these cyclization reactions is depicted in scheme 3. The reactions proceed *via* the formation of intermediate **5** through Ugi-4CR. There are two feasible pathways from **5** in different

solvents. Initially, the carbanion is formed by the addition of the base. (Scheme 3) It is reasonable to assume that the intramolecular nucleophilic addition of carbanion to triple bond in Ugi product **5**, form the *β*- lactam skeleton in both solvents. But, it can act as an intermediate in MeOH and the attack of methoxide to the carbonyl group in *β*- lactam skeleton takes place immediately from the one direction to afford the pyrrolidine-2,5-dione with regioselectivity.



Scheme 3. Plausible mechanism for the formation of *β*- lactam **6(a-n)** and pyrrolidine-2,5-dione **7(a-o)** in methanol.

Formation of different products in various solvents, could be attributed this observation to the basicity of K_2CO_3 in MeCN and MeOH. Potassium carbonate in MeCN could deprotonate the acidic C(sp^3)-H in Ugi product, but in MeOH, methoxide anion is produced which is stronger nucleophile than K_2CO_3 and in addition to the deprotonating of C-H, it can activate the NH amide and so the second cyclization occurs.

In conclusion, we have developed a novel and efficient method for the synthesis of two distinct sets of functionalized *β*-lactams and pyrrolidine-2,5-dione from the same Ugi adducts **5** involving Ugi-4CR/cyclization sequence in metal-free reaction conditions. Good to excellent yields, short reaction times, easy work-up, and high bond forming efficiency, atom economy and application of this approach in combinatorial chemistry are the advantages of this approach.

Experimental Section

General information

High resolution mass spectra were recorded on Mass-ESI-POS and Mass-ESI-NEG (FT-ICR) spectrometer.

General procedure for the synthesis of polysubstituted *β*-lactams (6a-n) through sequential Ugi-4CR/ cyclization

To a solution of aldehyde **1**(1 mmol) in MeOH (5 ml) was added aniline as a primary amine **2** (1 mmol), and the reaction mixture was stirred at room temperature (25°C) for 1 h. Then phenyl acetylene carboxylic acid **3** (1 mmol) was added and stirring was continued for 15 min, followed by addition of isocyanid **4** (1 mmol). The mixture was stirred for 24 h. The progress of the reaction was monitored using TLC (petroleum ether/ EtOAc 3:1). After completion of reaction, the *N*-substituted-2-alkynamides **5** was precipitated, separated and was transferred to a flask which contained 10 ml MeCN. Then K_2CO_3 (1 eq) was added to the mixture and the mixture was heated under reflux condition for 1-2 h. The progress of reaction was monitored using TLC (hexane/ EtOAc 4:1). After cooling to room temperature the desired product was precipitated, the yellowish sediment was filtered.

(*E*)-3-benzylidene-*N*-(tert-butyl)-4-oxo-1,2-diphenylazetidine-2-carboxamide (6a):

White powder; 385 mg(94%), m.p.: 172-173 °C; IR (KBr, cm^{-1}): υ =1670, 1749, 3343; ^{1}H NMR ($CDCl_3$,300 MHz): δ(ppm) = 1.22 (*s*, 9H, *t*-Bu), 6.09 (*s*, 1H, NH), 7.03 (*td*, *J* = 7.4, 0.9 Hz, 1H, H-Ar), 7.20-7.39 (*m*, 11H, H-Ar, C=CH), 7.52 (*d*, *J* = 8.1 Hz, 2H, H-Ar), 7.65 (*dd*, *J* = 7.2, 1.1 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 28.3, 52.0, 76.6, 118.3, 124.5, 126.5, 128.3, 128.7, 128.9, 128.9, 129.1, 130.2, 130.6, 131.9, 134.8, 136.7, 141.0,

163.0, 166.2; Mass: HR-MS (ESI-POS) = Calc. for $C_{27}H_{27}N_2O_2$ $[M+H]^+$ 411.20676, Found 411.20670. Calc. for $C_{27}H_{26}N_2NaO_2$ $[M+Na]^+$ 433.18871, Found 433.18865.

(*E*)-3-benzylidene-*N*-(tert-butyl)-2-(3-nitrophenyl)-4-oxo-1-phenylazetidine-2-carboxamide(6b):

White powder; 337 mg(74%), m.p.: 182-184 °C; IR (KBr, cm^{-1}): υ = 1673, 1740, 3383; ^1H NMR ($CDCl_3$, 300 MHz): δ(ppm) = 1.30 (*s*, 9H, *t*-Bu), 6.34 (*s*, 1H, NH), 7.08 (*t*, *J* = 7.3 Hz, 1H, H-Ar), 7.25-7.54 (*m*, 10H, H-Ar, C=CH), 7.97 (*d* , *J* = 7.8 Hz, 1H, H-Ar), 8.14 (*d*, *J* = 8.2 Hz, 1H, H-Ar), 8.60 (*s*, 1H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 28.4, 52.5, 74.6, 118.0, 123.9, 125.1, 128.1, 128.9, 129.4, 129.7, 130.7, 130.8, 131.1, 134.4, 136.0, 136.6, 139.6, 148.3, 162.5, 165.5; Mass: HR-MS (ESI-POS) = Calc. for $C_{27}H_{26}N_3O_4$ $[M+H]^+$ 456.19182, Found 456.1917 Calc. $C_{27}H_{25}N_3NaO_4$ $[M+Na]^+$ 478.17377, Found 478.17373

(*E*)-3-benzylidene-*N*-(tert-butyl)-4-oxo-1-phenyl-2-(pyridin-3-yl)azetidine-2-carboxamide (6c):

White powder; 366 mg(89%), m.p.: 161-162 °C; IR (KBr, cm^{-1}): υ = 1675, 1744, 3339; ^1H NMR ($CDCl_3$, 300 MHz): δ(ppm) = 1.27 (*s*, 9H, *t*-Bu), 6.25 (*s*, 1H, NH), 7.07 (*t*, *J* = 7.4 Hz, 1H, H-Ar), 7.21-7.37 (*m*, 7H, H-Ar, C=CH), 7.44 (*d*, *J* = 6.5 Hz, 2H, H-Ar), 7.47 (*d*, *J* = 8.2 Hz, 2H, H-Ar), 7.95 (*d*, *J* = 9.3 Hz, 1H, H-Ar), 8.53 (*d*, *J* = 4.7 Hz, 1H, H-Ar), 8.93 (*s*, 1H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 28.3, 52.3, 74.3, 118.1, 123.3, 125.0, 127.8, 128.8, 129.2, 130.4, 130.6, 130.7,131.3, 136.1, 136.2, 139.6, 149.9, 150.0, 162.6, 165.6; Mass: HR-MS (ESI-POS) = Calc. for $C_{26}H_{26}N_3O_2$ $[M+H]^+$ 412.20195, Found 412.20195. Calc. $C_{26}H_{25}N_3NaO_2$ $[M+Na]^+$ 434.18391, Found 434.18390.

(*E*)-3-benzylidene-*N*-(tert-butyl)-4-oxo-1-phenyl-2-(4-(trifluoromethyl)phenyl)azetidine-2-carboxamide (6d):

White powder; 392 mg(82%), m.p.: 164-166 °C; IR (KBr, cm^{-1}): υ = 1670, 1751, 3349; ^1H NMR ($CDCl_3$, 300 MHz): δ(ppm) = 1.27 (*s*, 9H, *t*-Bu), 6.23 (*s*, 1H, NH), 7.08 (*t*, *J* = 7.1 Hz, 1H, H-Ar), 7.24-7.34 (*m*, 6H, H-Ar, C=CH), 7.41 (*d* , *J* = 6.7 Hz, 2H, H-Ar), 7.48 (*d*, *J* = 8.4 Hz, 2H, H-Ar), 7.59 (*d*, *J* = 8.2 Hz, 2H, H-Ar), 7.80 (*d*, *J* = 8.2 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 28.3, 52.3, 75.4, 118.1, 124.9, 125.7, 127.5, 128.8, 128.9, 129.2, 130.6, 130.7, 131.2, 131.3, 136.2, 138.5, 140.0, 162.7, 165.7;Mass: HR-MS (ESI-POS) =

Calc. for $C_{28}H_{26}F_3N_2O_2$ $[M+H]^+$ 479.19417, Found 479.19409. Calc. $C_{28}H_{25}F_3N_2NaO_2$ $[M+Na]^+$ 501.17613, Found 501.17603.

(*E*)-3-benzylidene-*N*-(tert-butyl)-2-(4-cyanophenyl)-4-oxo-1-phenylazetidine-2-carboxamide (6e):

White powder; 287 mg(66%), m.p.: 182-184 °C; IR (KBr, cm^{-1}): υ = 1670, 1751, 3349; ^1H NMR ($CDCl_3$,300 MHz): δ(ppm) = 1.27 (*s*, 9H, *t*-Bu), 6.25 (*s*, 1H, NH), 7.09 (*t*, *J* = 7.4 Hz, 1H, H-Ar), 7.24-7.35 (*m*, 6H, H-Ar, C=CH), 7.42 (*t* , *J* = 7.7 Hz, 4H, H-Ar), 7.61 (*d*, *J* = 7.4 Hz, 2H, H-Ar), 7.79 (*d*, *J* = 8.4 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 28.3, 52.4, 75.0, 112.8, 118.0, 118.2, 125.1, 127.9, 128.8, 129.3, 130.7, 130.8, 131.1, 132.4, 136.0, 139.6, 139.7, 162.6, 165.4; Mass: HR-MS (ESI-POS) = Calc. for $C_{28}H_{26}N_3O_2$ $[M+H]^+$ 436.20202, Found 436.20195. Calc. $C_{28}H_{25}N_3NaO_2$ $[M+Na]^+$ 458.18398, Found 458.18390.

(*E*)-3-benzylidene-*N*-(tert-butyl)-4-oxo-1-phenyl-2-(pyridin-2-yl)azetidine-2-carboxamide (6f):

White powder; 263 mg(64%), m.p.: 159-161 °C; IR (KBr, cm^{-1}): υ = 1673, 1755, 3214, 3429; ^1H NMR ($CDCl_3$, 300 MHz): δ(ppm) = 1.35 (*s*, 9H, *t*-Bu), 7.02 (*t*, *J* = 7.4 Hz, 1H, H-Ar), 7.13 (*s*, 1H, NH), 7.21-7.69 (*m*, 12H, H-Ar, H-pyrid, C=CH), 8.63 (*d*, *J* = 4.7 Hz, 1H, H-Ar), 9.67 (*s*, 1H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 28.5, 51.8, 73.2, 117.3, 123.4, 123.5, 124.1, 125.6, 128.4, 129.0, 129.8, 130.3, 132.1, 137.0, 138.2, 142.1, 147.7, 156.1, 162.7, 165.0; Mass: HR-MS (ESI-POS) = Calc. for $C_{26}H_{26}N_3O_2$ $[M+H]^+$ 412.20195, Found 412.20195. Calc. for $C_{26}H_{25}N_3NaO_2$ $[M+Na]^+$ 434.18393, Found 434.18390. Calc. for $C_{26}H_{25}KN_3O_2$ $[M+K]^+$ 450.15787, Found 450.15784.

(*E*)-3-benzylidene-*N*-cyclohexyl-4-oxo-1-phenyl-2-(4-(trifluoromethyl)phenyl)azetidine-2-carboxamide (6g):

White powder; 317 mg(63%), m.p.: 166-168 °C; IR (KBr, cm^{-1}): υ = 1668, 1750, 3342; ^1H NMR ($CDCl_3$, 300 MHz): δ(ppm) = 1.00-1.88 (*m*, 10H, H-cyclohexyl), 3.85-3.95 (m, 1H, N-CH), 6.34 (*d*, *J* = 7.5, 1H, NH), 7.08 (*t*, *J* = 7.3 Hz, 1H, H-Ar), 7.24-7.46 (*m*, 10H, H-Ar, C=CH), 7.58 (*d*, *J* = 8.2 Hz, 2H, H-Ar), 7.83 (*d* , *J* = 8.1 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 24.5, 25.2, 32.4, 32.6, 48.9, 74.9, 118.0, 124.9, 125.5, 125.7, 127.9, 128.7, 128.9, 129.3, 130.7, 130.9, 131.2, 136.1, 138.2, 139.6, 162.8, 165.5; Mass: HR -MS

(ESI-POS) = Calc. for $C_{30}H_{28}F_3N_2O_2$ $[M+H]^+$ 505.20978, Found 505.20974. Calc. for $C_{30}H_{27}F_3N_2NaO_2$ $[M+Na]^+$ 527.19168, Found 527.19168. Calc. for $C_{30}H_{27}F_3KN_2O_2$ $[M+K]^+$ 543.16567, Found 543.16562.

(*E*)-3-benzylidene-*N*-(tert-butyl)-4-oxo-1-phenyl-2-(thiophen-2-yl)azetidine-2-carboxamide (6h):

Yellow powder; 374 mg(90%), m.p.: 174-176 °C; IR (KBr, cm^{-1}): υ = 1670, 1749, 3338; ^1H NMR ($CDCl_3$, 300 MHz): δ(ppm) = 1.24 (*s*, 9H, *t*-Bu), 6.23 (*s*, 1H, NH), 6.92 (*t*, *J* = 4.6 Hz, 1H, H-thienyl), 7.08 (*t*, *J* = 7.5 Hz, 1H, H-Ar), 7.18 (*s*, 1H, =CH), 7.26-7.53 (*m*, 11H, H-Ar, H-thienyl); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 28.2, 52.2, 72.2, 117.9, 124.7, 126.6, 126.8, 128.2, 128.7, 128.8, 129.1, 130.4, 130.9, 131.5, 136.2, 136.3, 141.3, 162.6, 166.1; Mass: HR-MS (ESI-POS) = Calc. for $C_{25}H_{25}N_2O_2S$ $[M+H]^+$ 417.16319, Found 417.16313. Calc. $C_{25}H_{24}N_2NaO_2S$ $[M+Na]^+$ 439.14515, Found 439.14507.

(*E*)-3-benzylidene-*N*-(tert-butyl)-2-(4-chlorophenyl)-4-oxo-1-phenylazetidine-2-carboxamide (6i):

White powder; 422 mg(95%), m.p.: 184-185 °C; IR (KBr, cm^{-1}): υ = 1671, 1747, 3341,3341; ^1H NMR ($CDCl_3$, 300 MHz): δ(ppm) = 1.24 (*s*, 9H, *t*-Bu), 6.17 (*s*, 1H, NH), 7.06 (*t*, *J* = 7.0 Hz, 1H, H-Ar), 7.21-7.35 (*m*, 8H, H-Ar, C=CH), 7.41 (*d*, *J* = 6.8 Hz, 2H, H-Ar), 7.48 (*d*, *J* = 7.9 Hz, 2H, H-Ar), 7.61 (*d*, *J* = 8.4 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 28.3, 52.2, 75.6, 118.2, 124.8, 127.1, 128.8, 129.0, 129.1, 129.8, 130.5, 130.7, 131.5, 133.1, 135.0, 136.3, 140.4, 162.8, 165.8; Mass: HR-MS (ESI-POS) = Calc. for $C_{27}H_{26}ClN_2O_2$ $[M+H]^+$ 445.16781, Found 445.16773. Calc. $C_{27}H_{25}ClN_2NaO_2$ $[M+Na]^+$ 467.14977, Found 467.14968. colourless crystal (polyhedron), dimensions 0.170 x 0.110 x 0.110 mm^3, crystal system monoclinic, space group C2/c, Z=8, a=25.069(3) Å, b=10.0489(12) Å, c=20.245(2) Å, alpha=90 deg, beta=110.317(2) deg, gamma=90 deg, V=4782.8(10) $Å^3$, rho=1.236 g/cm^3, T=200(2) K, $Theta_{max}$= 25.027 deg, radiation Mo Kalpha, lambda=0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 10.42and a completeness of 99.9% to a resolution of 0.84Å, 44807 reflections measured, 4210 unique (R(int)=0.0469), 3255 observed (I > 2σ (I)), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS based on the Laue symmetry of the reciprocal space, mu=0.19mm^{-1},

T_{min}=0.90, T_{max}=0.99, structure refined against F^2 with a Full-matrix least-squares algorithm using the SHELXL (Version 2014-1) software, 407 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.14 for observed reflections, final residual values R1(F)=0.057, wR(F^2)=0.133 for observed reflections, residual electron density -0.23 to 0.24 eÅ^{-3}. CCDC 991555 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(*E*)-3-benzylidene-*N*-(tert-butyl)-4-oxo-1-phenyl-2-(3,4,5-trimethoxyphenyl)azetidine-2-carboxamide (6j):

White powder; 400 mg(80%), m.p.: 136-138 °C; IR (KBr, cm^{-1}): υ = 3368, 3327, 1740, 1673; ^{1}H NMR ($CDCl_3$, 300 MHz): δ(ppm) = 1.19 (*s*, 9H, t-Bu), 3.70 (*s*, 6H, OMe), 3.83 (*s*, 3H, OMe), 6.04 (*s*, 1H, NH), 6.82 (*s*, 2H, H-Ar), 7.06 (*t*, *J* = 7.3 Hz, 1H, H-Ar), 7.23-7.38 (*m*, 8H, H-Ar, C=CH), 7.54 (*d*, *J* = 8.2 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 28.2, 52.0, 56.1, 60.9, 105.4, 118.4, 124.7, 126.3, 128.8, 128.9, 130.2, 130.4, 132.1, 136.8, 138.4, 141.2, 153.3, 162.8, 166.4; Mass: HR-MS (ESI-POS) = Calc. for $C_{30}H_{33}N_2O_5$ $[M+H]^+$ 501.23807, Found 501.23807. Calc. $C_{30}H_{32}N_2NaO_5$ $[M+Na]^+$ 523.22021., Found 523.22023. Calc. $C_{30}H_{32}KN_2O_5$ $[M+K]^+$ 539.19422, Found 539.19423.

(*E*)-3-benzylidene-1-(4-bromophenyl)-*N*-(tert-butyl)-4-oxo-2-phenylazetidine-2-carboxamide (6k):

White powder; 464 mg(95%), m.p.: 212-214 °C; IR (KBr, cm^{-1}): υ = 3337, 1750, 1674; ^{1}H NMR ($CDCl_3$,300 MHz): δ(ppm) = 1.19 (*s*, 9H, t-Bu), 6.00 (*s*, 1H, NH), 7.26-7.30 (*m*, 6H, H-Ar, -C=CH), 7.32-7.33 (*m*, 2H, H-Ar), 7.36-7.41 (*m*, 3H, H-Ar), 7.43-7.47 (*m*, 2H, H-Ar), 7.59-7.63 (*m*, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 28.3, 52.1, 76.8, 117.2, 119.9, 126.6, 128.0, 128.9, 129.2, 129.4, 130.3, 130.4, 131.8, 134.8, 135.9, 141.3, 162.6, 165.9; Mass: HR-MS (ESI-POS) = Calc. for $C_{27}H_{26}{}^{79}BrN_2O_2$ $[M+H]^+$ 489.11721, Found 489.11721.

(*E*)-3-benzylidene-*N*-cyclohexyl-4-oxo-1-phenyl-2-(p-tolyl)azetidine-2-carboxamide (6l):

White powder; 373 mg(83%), m.p.: 154-156 °C; IR (KBr, cm^{-1}): υ = 3337, 1746, 1670; ^{1}H NMR ($CDCl_3$,300 MHz): δ(ppm) = 0.95-1.07 (*m*, 3H, H-cyclohexyl), 1.25-1.32 (*m*, 2H, H-cyclohexyl), 1.50-1.52 (*m*, 3H, H-Ar), 1.75-1.84 (*m*, 2H, H-Ar), 2.30 (*s,* 1H, -Me), 3.83-3.92

(*m*, 1H, CH- cyclohexyl), 6.19 (*d*, *J* = 7.8, Hz, 1H, NH), 7.03 (*t*, *J* = 7.4 Hz, 1H, H-Ar), 7.14 (*d*, *J* = 8.1 Hz, 2H, H-Ar), 7.21-7.31 (*m*, 6H, H-Ar, C=CH), 7.44-7.56 (*m*, 6H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 21.2, 24.4, 25.3, 32.3, 32.6, 48.6, 76.1, 118.2, 124.5, 126.9, 128.2, 128.6, 129.0, 129.6, 130.2, 130.9, 131.2, 131.7, 136.6, 139.0, 140.5, 163.2, 166.2; Mass: HR-MS (ESI-POS) = Calc. for $C_{30}H_{31}N_2O_2$ $[M+H]^+$ 451.23834, Found 451.23828. Calc. $C_{30}H_{30}N_2NaO_2$ $[M+Na]^+$ 473.22036, Found 473.22029. Calc. $C_{30}H_{30}KN_2O_2$ $[M+K]^+$ 489.19436, Found 489.19428.

(*E*)-3-benzylidene-*N*-cyclohexyl-4-oxo-1,2-diphenylazetidine-2-carboxamide (6m):

Yellow powder; 388 mg(89%), m.p.: 150-152 °C; IR (KBr, cm^{-1}): υ = 3358, 1737, 1669; ^{1}H NMR ($CDCl_3$,300 MHz): δ(ppm) = 0.87-1.12 (*m*, 3H, H-cyclohexyl), 1.27-1.36 (*m*, 2H, H-cyclohexyl), 1.51-1.53 (*m*, 3H, H-cyclohexyl), 1.78-1.86 (*m*, 2H, H-cyclohexyl), 3.83-3.95 (*m*, 1H, CH- cyclohexyl), 6.24 (*d*, *J* = 7.7, Hz, 1H, NH), 7.04 (*t*, *J* = 7.0 Hz, 1H, H-Ar), 7.18-7.29 (*m*, 6H, H-Ar), 7.31-7.38 (*m*, 3H, H-Ar, C=CH), 7.40 (*d*, *J* = 7.7 Hz, 2H, H-Ar), 7.49 (*d*, *J* = 8.4 Hz, 2H, H-Ar), 7.67 (*d*, *J* = 7.1 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 24.4, 25.3, 32.3, 32.6, 48.7, 76.1, 115.4, 118.2, 124.6, 127.2, 128.3, 128.6, 128.9, 129.0, 129.1, 129.5, 130.3, 130.9, 131.6, 134.3, 136.5, 140.3, 163.1, 166.1; Mass: HR-MS (ESI-POS) = Calc. for $C_{29}H_{29}N_2O_2$ $[M+H]^+$ 437.22209, Found 437.22214. Calc. $C_{29}H_{28}N_2NaO_2$ [M+Na] + 459.20408, Found 459.20412. Calc. $C_{29}H_{28}KN_2O_2$ $[M+K]^+$ 475.17806, Found 475.17809.

(*E*)-3-benzylidene-*N*-(tert-butyl)-1-(4-isopropylphenyl)-4-oxo-2-phenylazetidine-2-carboxamide (6n):

White powder; 393 mg(87%), m.p.: 162-164 °C; IR (KBr, cm^{-1}): υ = 3351, 1740, 1670; ^{1}H NMR ($CDCl_3$,300 MHz): 1.17 (*d*, *J* = 6.9 Hz, 6H, -CH3), 1.22 (*s*, 9H, t-Bu), 2.78-2.83 (*m*, 1H, -CH), 6.09 (*s*, 1H, NH), 7.08 (*d*, *J* = 8.5 Hz, 2H, H-Ar), 7.23-7.29 (*m*, 4H, H-Ar), 7.30-7.39 (*m*, 5H, H-Ar, C=CH), 7.42 (*d*, *J* = 8.5 Hz, 2H, H-Ar), 7.65 (*d*, , *J* = 6.2 Hz, 2H, H-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) = 23.8, 23.9 28.3, 33.6, 52.0, 118.4, 126.1, 126.9, 128.3, 128.7, 128.9, 129.0, 130.1, 130.5, 131.9, 134.4, 135.0, 141.1, 145.2, 162.8, 166.3; Mass: HR-MS (ESI-POS) = Calc. for $C_{30}H_{33}N_2O_2$ $[M+H]^+$ 453.25344, Found 453.25348. Calc. $C_{30}H_{32}N_2NaO_2$ $[M+Na]^+$ 475.23552, Found 475.23553. Calc. $C_{30}H_{32}KN_2O_2$ $[M+K]^+$ 491.20949, Found 491.20950.

General procedure for the synthesis of poly substituted pyrrolidine-2,5-dione through One-pot Ugi 4CR/cyclization (7a-o)

To a solution of aldehyde 1(1 mmol) in MeOH (5 ml) was added aniline as a primary amine 2 (1 mmol), and the reaction mixture was stirred at room temperature (25 °C) for 1 h. Then phenyl acetylene carboxylic acid 3 (1 mmol) was added and stirring was continued for 15 min, followed by addition of isocyanid 4 (1 mmol). The mixture was stirred for 24 h. The progress of the reaction was monitored using TLC (petroleum ether/ EtOAc 3:1). After completion of reaction, K_2CO_3 (1 eq) was added to the mixture and then the mixture was heated under reflux for 1-2 h. Reaction progress was monitored using TLC (hexane/ EtOAc 4:1). After cooling to room temperature the desired product was precipitated, the yellowish sediment was filtered.

(*R*,*E*)-4-benzylidene-1-(tert-butyl)-3-phenyl-3-(phenylamino)pyrrolidine-2,5-dione (7a):

Yellow powder, 385 mg(94%), m.p.:171-173°C, IR(KBr, cm^{-1}): υ= 3389, 1763, 1698. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.50 (*s*, 9H, t-Bu), 4.45 (*s*, 1H, -NH), 6.28 (*d*, 2H, *J* = 8.3 Hz, H-Ar), 6.72 (*t*, 1H, *J* = 7.0 Hz, H-Ar), 7.17 (*t*, 2H, *J* = 7.4 Hz, H-Ar), 7.23-7.28 (*m*, 1H, H-Ar), 7.33 (*d*, 2H, *J* = 7.3 Hz, H-Ar), 7.40-7.47 (*m*, 3H, H-Ar), 7.73 (*d*, 2H, *J* = 8.1 Hz, H-Ar), 7,93 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 28.3, 59.1, 67.2, 116.4, 120.0, 126.3, 128.1, 128.6, 128.7, 129.1, 129.4, 129.9, 131.0, 133.1, 138.2, 138.5, 144.1, 170.6, 176.5. Mass: HR-MS (ESI-POS) = Calc. for $C_{27}H_{27}N_2O_2$ [M+H]+ 411.20700, Found 411.20694. Calc. for $C_{27}H_{26}N_2NaO_2$ $[M+Na]^+$ 433.18908, Found 433.18900. Calc. for $C_{27}H_{26}KN_2O_2$ $[M+K]^+$ 449.16301, Found 449.16293.

(*R*,*E*)-4-benzylidene-1-(tert-butyl)-3-(4-chlorophenyl)-3-(phenylamino)pyrrolidine-2,5-dione (7b):

Yellow powder, 404 mg(91%), m.p.: 197-199 °C, IR(KBr, cm^{-1}): υ= 1705, 1768, 3424. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.56 (*s*, 9H, t-Bu), 4.36 (*s*, 1H, -NH), 6.29 (*d*, 2H, *J* = 8.0 Hz, H-Ar), 6.74 (*t*, 1H, *J* = 7.3 Hz, H-Ar), 6.98 (*t*, 2H, *J* = 7.8 Hz, H-Ar), 7.20 (*t*, 2H, *J* = 7.3 Hz, H-Ar), 7.27 (*d*, 1H, *J* = 5.6 Hz, H-Ar), 7.33 (*d*, 2H, *J* = 7.3 Hz, H-Ar), 7.39 (*d*, 2H, *J* = 8.5 Hz, H-Ar), 7.64 (*d*, 2H, *J* = 8.5 Hz, H-Ar), 7.91 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 28.3, 59.2, 66.8, 116.9, 120.5, 127.8, 128.2, 128.8, 129.5, 130.1, 131.0, 132.9, 135.2, 137.0, 138.6, 143.8, 170.4, 176.2. Mass: HR-MS (ESI-NEG) = Calc. for $C_{27}H_{26}ClN_2O_2$ $[M+H]^+$ 445.16745, Found 445.16750. Calc. for $C_{27}H_{25}ClKN_2O_2$ [M+K]+ 483.12336, Found 483.12340. yellow crystal (polyhedron), dimensions .18 x .10 x .10 mm^3, crystal system

monoclinic, space group $P2_1/n$, Z=4, a=12.8190(6) Å, b=10.5217(5) Å, c=18.1283(8) Å, alpha=90 deg, beta=106.9487(12) deg, gamma=90 deg, V=2338.90(19) $Å^3$, rho=1.264 g/cm^3, T=200(2) K, $Theta_{max}$= 25.106 deg, radiation Mo Kalpha, lambda=0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 6.74and a completeness of 99.5% to a resolution of 0.84Å, 28777 reflections measured, 4154 unique (R(int)=0.0445), 3053 observed ($I > 2\sigma$ (I)), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS based on the Laue symmetry of the reciprocal space, mu=0.19mm^{-1}, T_{min}=0.89, T_{max}=0.96, structure refined against F^2 with a Full-matrix least-squares algorithm using the SHELXL (Version 2014-1) software, 292 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.06 for observed reflections, final residual values R1(F)=0.064, wR(F^2)=0.155 for observed reflections, residual electron density -0.30 to 0.58 e$Å^{-3}$. CCDC 991554 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

_R,E_)-4-(4-benzylidene-1-(tert-butyl)-2,5-dioxo-3-(phenylamino)pyrrolidin-3-yl)benzonitrile (7c):

Yellow powder, 365 mg(84%), m.p.:235-237 °C, IR(KBr, cm^{-1}): υ= 3385, 1766, 1704,. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.54 (*s*, 9H, t-Bu), 4.45 (*s*, 1H, -NH), 6.45 (*d*, 2H, *J* = 7.9 Hz, H-Ar), 6.84 (*t*, 1H, *J* = 7.3 Hz, H-Ar), 7.04 (*t*, 2H, *J* = 7.8 Hz, H-Ar), 7.21 (*t*, 2H, *J* = 7.3 Hz, H-Ar), 7.26-7.32 (*m*, 1H, H-Ar), 7.40 (*d*, 2H, *J* = 7.3 Hz, H-Ar), 7.67 (*d*, 2H, *J* = 8.4 Hz, H-Ar), 7.77 (*d*, 2H, *J* = 8.4 Hz, H-Ar), 7,94 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 28.2, 59.5, 67.4, 112.9, 118.1, 118.5, 121.7, 127.3, 128.0, 128.3, 128.9, 130.4, 131.1, 132.6, 132.8, 139.4, 143.3, 143.4, 170.2, 176.0. Mass: HR-MS (ESI-POS) = Calc. for $C_{28}H_{26}N_3O_2$ $[M+H]^+$ 436.20262, Found 436.20250. Calc. for $C_{28}H_{25}N_3NaO_2$ $[M+Na]^+$ 458.18468, Found 458.18454.

(_R,E_)-4-benzylidene-1-(tert-butyl)-3-(phenylamino)-3-(4 trifluoromethyl)phenyl)pyrrolidine-2,5-dione (7d):

Yellow powder, 464 mg(97%), m.p.:175-177 °C, IR(KBr, cm^{-1}): υ= 3438, 1772, 1705. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.56 (*s*, 9H, t-Bu), 4.44 (*s*, 1H, -NH), 6.38 (*d*, 2H, *J* = 7.9 Hz, H-Ar), 6.79 (*t*, 1H, *J* = 7.3 Hz, H-Ar), 7.02 (*t*, 2H, *J* = 7.8 Hz, H-Ar), 7.20 (*t*, 2H, *J* = 7.34 Hz,

H-Ar), 7.29 (*t*, 1H, *J* = 7.3 Hz, H-Ar), 7.37 (*d*, 2H, *J* = 7.2 Hz, H-Ar), 7.67 (*d*, 2H, *J* = 8.4 Hz, H-Ar), 7.82 (*d*, 2H, *J* = 8.3 Hz, H-Ar), 7.95 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 28.2, 59.3, 67.2, 117.6, 121.1, 126.1 (CF_3), 126.9, 128.1, 128.3, 128.8, 130.2, 130.9, 131.1, 131.3, 132.7, 139.0, 142.2, 143.6, 170.3, 176.1. Mass: HR-MS (ESI-NEG) = Calc. for $C_{28}H_{24}F_3N_2O_2$ $[M+H]^-$ 477.17984, Found 477.17979. yellow crystal (polyhedron), dimensions 0.290 x 0.180 x 0.120 mm^3, crystal system triclinic, space group $P\bar{1}$, Z=2, a=10.7819(15) Å, b=11.2776(18) Å, c=12.123(3) Å, alpha=114.810(4) deg, beta=97.625(4) deg, gamma=108.463(3) deg, V=1207.3(4) $Å^3$, rho=1.316 g/cm^3, T=200(2) K, $Theta_{max}$= 24.854 deg, radiation Mo Kalpha, lambda=0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 3.36and a completeness of 99.0% to a resolution of 0.85Å, 14048 reflections measured, 4147 unique (R(int)=0.0280), 3168 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS based on the Laue symmetry of the reciprocal space, mu=0.10mm^{-1}, T_{min}=0.91, T_{max}=0.96, structure refined against F^2 with a Full-matrix least-squares algorithm using the SHELXL (Version 2013-4) software, 347 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.05 for observed reflections, final residual values R1(F)=0.043, wR(F^2)=0.096 for observed reflections, residual electron density -0.22 to 0.32 e$Å^{-3}$. CCDC 991553 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(*R,E*)-4-benzylidene-1-(tert-butyl)-3-(phenylamino)-3-(p-tolyl)pyrrolidine-2,5-dione (7e):

Yellow powder, 365 mg(86%), m.p.:153-155 °C, IR(KBr, cm^{-1}): υ= 3054, 1768, 1704. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.58 (*s*, 9H, t-Bu), 2.38 (*s*, 3H, -CH3), 4.40 (*s*, 1H, -NH), 6.24 (*d*, 2H, *J* = 7.9 Hz, H-Ar), 6.69 (*t*, 1H, *J* = 7.3 Hz, H-Ar), 6.96 (*t*, 2H, *J* = 7.8 Hz, H-Ar), 7.17 (*t*, 2H, *J* = 7.3 Hz, H-Ar), 7.22-7.27 (*m*, 3H, H-Ar), 7.32 (*d*, 2H, *J* = 7.2 Hz, H-Ar), 7.60 (*d*, 2H, *J* = 8.2 Hz, H-Ar), 7.91 (*s*, 1H, =CH). 13C-NMR (75 MHz, $CDCl_3$): δ 21.1, 28.3, 59.0, 66.9, 116.1, 119.8, 126.2, 128.0, 128.7, 129.7, 130.0, 131.0, 133.1, 135.6, 137.9, 139.0, 144.1, 170.6, 176.5. Mass: HR-MS (ESI-POS) = Calc. for $C_{28}H_{29}N_2O_2$ $[M+H]^+$ 425.22272, Found 425.22265. Calc. for $C_{28}H_{28}N_2NaO_2$ $[M+Na]^+$ 447.20475, Found 447.20467. Calc. for $C_{28}H_{28}KN_2O_2$ $[M+K]^+$ 463.17870, Found 463.17862.

(*R,E*)-4-benzylidene-1-cyclohexyl-3-phenyl-3-(phenylamino)pyrrolidine-2,5-dione (7f):

Yellow powder, 362 mg(83%), m.p.:197-199 °C, IR(KBr, cm^{-1}): υ= 3290, 1757, 1696. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.19-1.33 (*m*, 3H, H-cyclohexyl), 1.52-1.67 (*m*, 3H, H-cyclohexyl), 1.79-1.82 (*m*, 2H, H-cyclohexyl), 2.08-2.21 (*m*, 2H, H-cyclohexyl), 4.05-4.13 (*m*, 1H, N-CH), 4.45 (*s*, 1H, -NH), 6.29 (*d*, 2H, *J* = 7.9 Hz, H-Ar), 6.73 (*t*, 1H, *J* = 7.3 Hz, H-Ar), 6.97 (*t*, 2H, *J* = 7.8 Hz, H-Ar), 7.19 (*t*, 2H, *J* = 7.3 Hz, H-Ar), 7.25-7.30 (*m*, 1H, H-Ar), 7.34 (*d*, 2H, *J* = 7.4 Hz, H-Ar), 7.40-7.43 (*m*, 3H, H-Ar), 7.72(*d*, 2H, *J* = 6.2 Hz, H-Ar), 7.94 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.0, 25.7, 25.8, 28.6, 28.7, 52.2, 67.2, 116.6, 120.3, 126.3, 128.2, 128.7, 128.8, 129.1, 129.3, 130.0, 131.1, 131.4, 133.0, 138.4, 138.7, 144.1, 169.7, 175.8. Mass: HR-MS (ESI-POS) = Calc. for $C_{29}H_{29}N_2O_2$ $[M+H]^+$ 437.22204, Found 437.22210. Calc. for $C_{29}H_{28}N_2NaO_2$ $[M+Na]^+$ 459.20406, Found 459.20410. Calc. for $C_{29}H_{28}KN_2O_2$ $[M+K]^+$ 475.17794, Found 475.17799.

(*R,E*)-4-benzylidene-1-cyclohexyl-3-(phenylamino)-3-(4 (trifluoromethyl)phenyl)pyrrolidine-2,5-dione (7g):

Yellow powder, 454 mg(90%), m.p.:200-203 °C, IR(KBr, cm^{-1}): υ= 3410, 1769, 1708. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.23-1.33 (*m*, 3H, H-cyclohexyl), 1.52-1.67 (*m*, 3H, H-cyclohexyl), 1.80-1.83 (*m*, 2H, H-cyclohexyl), 2.05-2.18 (*m*, 2H, H-cyclohexyl), 4.03-4.12 (*m*, 1H, N-CH), 4.45 (*s*, 1H, -NH), 6.38 (*d*, 2H, *J* = 8.1 Hz, H-Ar), 6.80 (*t*, 1H, *J* = 7.3 Hz, H-Ar), 7.01 (*t*, 2H, *J* = 7.8 Hz, H-Ar), 7.23 (**t**, 1H, *J* = 7.2 Hz, H-Ar), 7.25 (*t*, 1H, *J* = 7.2 Hz, H-Ar), 7.31 (*t*, 1H, *J* = 7.2 Hz, H-Ar), 7.39 (*d*, 2H, *J* = 7.1 Hz, H-Ar), 7.66 (*d*, 1H, *J* = 8.4 Hz, H-Ar), 7.83 (*d*, 2H, *J* = 8.4 Hz, H-Ar), 7.947 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.9, 25.6, 25.7, 28.6, 28.7, 52.4, 67.3, 117.8, 121.3, 121.9, 126.2 (CF3), 126.9, 128.1, 128.4, 128.9, 130.4, 131.1, 132.7, 139.6, 142.1, 143.6, 169.4, 175.4. Mass: HR-MS (ESI-POS) = Calc. for $C_{30}H_{28}F_3N_2O_2$ $[M+H]^+$ 505.20942, Found 505.20947. Calc. for $C_{30}H_{27}F_3N_2NaO_2$ $[M+Na]^+$ 527.19170, Found 527.19170. Calc. for $C_{30}H_{27}F_3KN_2O_2$ $[M+K]^+$ 543.16568, Found 543.16567.

(*R,E*)-4-benzylidene-1-(tert-butyl)-3-(phenylamino)-3-(pyridin-3-yl)pyrrolidine-2,5-dione (7h):

Yellow powder, 279 mg(68%), m.p.:128-130 °C, IR(KBr, cm^{-1}): υ= 3390, 1761, 1702. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.51 (*s*, 9H, t-Bu), 5.0 (*brs*, 1H, -NH), 6.47 (*d*, 2H, *J* = 7.8 Hz, H-Ar), 6.81 (*t*, 1H, *J* = 7.2 Hz, H-Ar), 7.02 (*t*, 2H, *J* = 7.7 Hz, H-Ar), 7.08-7.28 (*m*, 4H, H-Ar), 7.36-7.47 (*m*, 3H, H-Ar), 7.84-7.99 (*m*, 3H, H-Ar, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 28.5, 36.5, 59.4, 116.0, 118.5, 120.1, 121.6, 127.6, 128.1, 128.3, 128.9, 129.1, 130.4, 131.3,

132.5, 135.0, 139.6, 143.5, 170.1, 176.3. Mass: HR-MS (ESI-POS) = Calc. for $C_{26}H_{26}N_3O_2$ $[M+H]^+$ 412.20166, Found 412.20166. Calc. for $C_{26}H_{25}N_3NaO_2$ $[M+Na]^+$ 434.18381, Found 434.18383. Calc. for $C_{26}H_{25}KN_3O_2$ $[M+K]^+$ 450.15770, Found 450.15772.

(*R,E*)-4-benzylidene-3-(4-chlorophenyl)-1-cyclohexyl-3-(phenylamino)pyrrolidine-2,5-dione (7i):

Yellow powder, 414 mg(88%), m.p.:185-187 °C, IR(KBr, cm^{-1}): υ= 3504, 1762, 1701. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.22-1.26 (*m*, 3H, H-cyclohexyl), 1.53-1.79 (*m*, 5H, H-cyclohexyl), 2.06-2.18 (*m*, 2H, H-cyclohexyl), 3.68-3.75 (*m*, 1H, N-CH), 4.38 (*s*, 1H, -NH), 6.30 (*d*, 2H, *J* = 7.5 Hz, H-Ar), 6.75 (*t*, 1H, *J* = 7.0 Hz, H-Ar), 6.98 (*t*, 2H, *J* = 7.3 Hz, H-Ar), 7.21-7.45 (*m*, 7H, H-Ar), 7.64 (*d*, 2H, *J* = 8.2 Hz, H-Ar), 7.93 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.8, 25.7, 25.8, 28.6, 28.7, 52.3, 66.9, 117.1, 120.8, 127.9, 128.2, 128.3, 128.8, 129.5, 130.2, 131.1, 132.8, 135.2, 136.8, 139.2, 143.8, 169.5, 175.6. Mass: HR-MS (ESI-POS) = Calc. for $C_{29}H_{28}ClN_2O_2$ $[M+H]^+$ 471.18383, Found 471.18375. Calc. for $C_{29}H_{27}ClN_2NaO_2$ $[M+Na]^+$ 493.16562, Found 493.16557. Calc. for $C_{29}H_{27}ClKN_2O_2$ $[M+K]^+$ 509.13969, Found 509.13962.

(*R,E*)-4-benzylidene-1-(tert-butyl)-3-((3,4-dimethylphenyl)amino)-3-phenylpyrrolidine-2,5-dione (7j):

Yellow powder, 333 mg(76%), m.p.:150-152 °C, IR(KBr, cm^{-1}): υ= 3394, 1761 1698. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.59 (*s*, 9H, t-Bu), 2.04 (*s*, 3H, -CH3), 2.08 (*s*, 3H, -CH3), 4.3 (*brs*, 1H, -NH), 6.10 (*d*, 1H, *J* = 8.0 Hz, H-Ar), 6.15 (*s*, 1H, H-Ar), 6.75 (*d*, 1H, *J* = 8.0 Hz, H-Ar), 7.18-7.30 (*m*, 3H, H-Ar), 7.39-7.41 (*m*, 5H, H-Ar), 7.69 (*d*, 2H, *J* = 6.9 Hz, H-Ar), 7.91 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.8, 19.9, 28.3, 59.0, 67.4, 114.6, 118.9, 126.3, 128.1, 128.6, 128.9, 129.2, 129.3, 129.8, 131.2, 131.4, 133.2, 136.8, 138.0, 138.6, 142.1, 170.9, 176.9. Mass: HR-MS (ESI-POS) = Calc. for $C_{29}H_{31}N_2O_2$ $[M+H]^+$ 439.23843, Found 439.23835. Calc. for $C_{29}H_{30}N_2NaO_2$ $[M+Na]^+$ 461.22063, Found 461.22051. Calc. for $C_{29}H_{30}KN_2O_2$ $[M+K]^+$ 477.19453, Found 477.19442.

(*R,E*)-4-benzylidene-1-cyclohexyl-3-(4-methoxyphenyl)-3-(phenylamino)pyrrolidine-2,5-dione (7k):

Yellow powder, 382 mg(82%), m.p.:156-158 °C, IR(KBr, cm^{-1}): υ= 3386, 1766, 1703. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.19-1.27 (*m*, 3H, H-cyclohexyl), 1.53-1.80 (*m*, 5H, H-cyclohexyl), 2.09-2.22 (*m*, 2H, H-cyclohexyl), 3.82 (*s*, 1H, -OMe), 4.09 (*t*, 1H, *J* = 11.5 Hz,

N-CH), 4.40 (*s*, 1H, -NH), 6.23 (*d*, 2H, *J* = 7.6 Hz, H-Ar), 6.70 (*t*, 1H, *J* = 7.2 Hz, H-Ar), 6.93-6.98 (*m*, 4H, H-Ar), 7.20 (*t*, 2H, *J* = 7.0 Hz, H-Ar), 7.28 (*t*, 1H, *J* = 7.0 Hz, H-Ar), 7.34 (*d*, 2H, *J* = 7.4 Hz, H-Ar), 7.66 (*d*, 1H, *J* = 7.3 Hz, H-Ar), 7.90 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.0, 25.7, 25.8, 28.6, 28.8, 52.1, 55.3, 66.6, 114.7, 116.1, 120.0, 127.8, 128.2, 128.7, 129.9, 130.3, 131.1, 133.0, 138.5, 144.2, 160.1, 169.7, 176.0. Mass: HR-MS (ESI-POS) = Calc. for $C_{30}H_{31}N_2O_3$ $[M+H]^+$ 467.23276, Found 467.23279. Calc. for $C_{30}H_{30}N_2NaO_3$ $[M+Na]^+$ 489.21470, Found 489.21473.

(*R,E*)-4-(4-benzylidene-1-cyclohexyl-2,5-dioxo-3-(phenylamino)pyrrolidin-3-yl)benzonitrile (7l):

Yellow powder, 332 mg(72%), m.p.:225-22 7°C, IR(KBr, cm^{-1}): υ= 3393, 1771, 1705. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.17-1.32 (*m*, 3H, H-cyclohexyl), 1.49-1.82 (*m*, 5H, H-cyclohexyl), 2.02-2.15 (*m*, 2H, H-cyclohexyl), 4.05 (*tt*, 1H, *J* = 12.3, 3.6 Hz, N-CH), 4.45 (*s*, 1H, -NH), 6.44 (*d*, 2H, *J* = 7.8 Hz, H-Ar), 6.84 (*t*, 1H, *J* = 7.3 Hz, H-Ar), 7.04 (*t*, 2H, *J* = 7.7 Hz, H-Ar), 7.24 (*t*, 2H, *J* = 7.4 Hz, H-Ar), 7.33 (*t*, 1H, *J* = 7.2 Hz, H-Ar), 7.42 (*d*, 2H, *J* = 7.3 Hz, H-Ar), 7.67 (*d*, 2H, *J* = 8.4 Hz, H-Ar), 7.79 (*d*, 2H, *J* = 8.4 Hz, H-Ar), 7.96 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.9, 25.6, 25.7, 28.6, 28.7, 52.4, 67.5, 113.0, 118.1, 118.6, 122.0, 127.3, 127.9, 128.4, 129.0, 129.2, 130.6, 131.2, 132.5, 132.8, 139.9, 143.1, 143.4, 169.2, 175.2. Mass: HR-MS (ESI-POS) = Calc. for $C_{30}H_{28}N_3O_2$ $[M+H]^+$ 462.21785, Found 462.21781.

(*R,E*)-4-benzylidene-3-(4-bromophenyl)-1-cyclohexyl-3-(phenylamino)pyrrolidine-2,5-dione (7m):

Yellow powder, 412 mg(81%), m.p.: 217-219°C, IR(KBr, cm^{-1}): υ= 3330, 3056, 1764, 1701. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.17-1.24 (*m*, 3H, H-cyclohexyl), 1.52-1.81 (*m*, 5H, H-cyclohexyl), 2.01-2.22 (*m*, 2H, H-cyclohexyl), 4.02-4.1 (*m*, 1H, N-CH), 4.39 (*s*, 1H, -NH), 6.29 (*d*, 2H, *J* = 7.7 Hz, H-Ar), 6.84 (*t*, 1H, *J* = 7.3 Hz, H-Ar), 7.04 (*t*, 2H, *J* = 7.7 Hz, H-Ar), 7.24 (*t*, 2H, *J* = 7.4 Hz, H-Ar), 6.75 (*t*, 1H, *J* = 7.1 Hz, H-Ar), 6.97 (*d*, 2H, *J* = 7.4 Hz, H-Ar), 7.20-7.30 (*m*, 3H, H-Ar), 7.35 (*d*, 2H, *J* = 7.3 Hz, H-Ar), 7.53 (*d*, 2H, *J* = 8.3 Hz, H-Ar), 7.58 (*d*, 2H, *J* = 8.3 Hz, H-Ar), 7.93 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 25.0, 25.6, 25.7, 28.6, 28.7, 52.3, 66.9, 117.1, 120.8, 123.5, 128.1, 128.2, 128.3, 128.8, 130.3, 131.1, 132.4, 132.8, 137.3, 139.3, 143.8, 169.5, 175.5. Mass: HR-MS (ESI-POS) = Calc. for $C_{29}H_{28}BrN_2O_2$ $[M+H]^+$ 515.13343, Found 515.13334. Calc. for $C_{29}H_{27}BrKN_2O_2$ $[M+K]^+$ 553.08932, Found 553.08923.

(*R*,*E*)-4-benzylidene-3-((4-bromophenyl)amino)-1-cyclohexyl-3-(p-tolyl)pyrrolidine-2,5-dione (7n):

Yellow powder, 439 mg(83%), m.p.:152-154°C, IR(KBr, cm^{-1}): υ= 3310, 3401, 1764, 1702. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.17-1.27 (*m*, 3H, H-cyclohexyl), 1.51-1.79 (*m*, 5H, H-cyclohexyl), 2.02-2.23 (*m*, 2H, H-cyclohexyl), 2.36 (*s*, 3H, -CH_3), 4.09 (*m*, 1H, N-CH), 4.43 (*s*, 1H, -NH), 6.06 (*d*, 2H, *J* = 8.4 Hz, H-Ar), 7.02 (*d*, 2H, *J* = 8.4 Hz, H-Ar), 7.16-7.28 (*m*, 7H, H-Ar), 7.58 (*d*, 2H, *J* = 7.9 Hz, H-Ar), 7.91 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.1, 25.0, 25.6, 25.7, 28.6, 28.8, 52.2, 66.8, 111.9, 117.3, 126.2, 128.1, 128.2, 130.1, 130.2, 130.9, 131.5, 132.8, 135.2, 138.7, 139.4, 143.2, 169.5, 175.6. Mass: HR-MS (ESI-POS) = Calc. for $C_{30}H_{30}{}^{79}BrN_2O_2$ $[M+H]^+$ 529.14932, Found 529.14919.

(*R*,*E*)-4-benzylidene-3-((4-bromophenyl)amino)-1-(tert-butyl)-3-phenylpyrrolidine-2,5-dione (7o):

Yellow powder, 361 mg(74%), m.p.:152-154°C, IR(KBr, cm^{-1}): υ= 3310, 3060, 1762, 1698. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.57 (*s*, 9H, *t*-Bu), 4.42 (*s*, 1H, -NH), 6.08 (*d*, 2H, *J* = 8.2 Hz, H-Ar), 7.05 (*d*, 2H, *J* = 8.2 Hz, H-Ar), 7.17 (*t*, 1H, *J* = 7.5 Hz, H-Ar), 7.18 (*d*, 1H, *J* = 6.8 Hz, H-Ar), 7.19-7.30 (*m*, 3H, H-Ar), 7.43-7.45 (*m*, 3H, H-Ar), 7.70 (*d*, 2H, *J* = 5.5 Hz, H-Ar), 7.92 (*s*, 1H, =CH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 28.3, 59.2, 67.1, 111.8, 117.3, 126.3, 127.9, 128.2, 129.4, 129.5, 130.0, 130.8, 131.5, 132.9, 138.3, 143.1, 170.3, 176.0. Mass: HR-MS (ESI-POS) = Calc. for $C_{27}H_{26}{}^{79}BrN_2O_2$ $[M+H]^+$ 489.11897, Found 489.11867. Calc. for $C_{27}H_{25}{}^{79}BrN_2NaO_2$ $[M+Na]^+$ 511.10132, Found 511.10097. Calc. for $C_{27}H_{25}{}^{79}BrKN_2O_2$ $[M+K]^+$ 527.07544, Found 527.07507.

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ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H-COSY 2D NMR, IR, HRMS spectra for compounds **6a-6n** and **7a-7o**; X-ray crystal data for compound **6i**, **7b** and **7d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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